Report of A Trip to Europe of Participation in an International Workshop on "Biological Monitoring of Workers Manufacturing, Formulating and Applying Pesticides" and Observation of Use of Methyl Bromide in Soil

By

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HS-1384 Revised August 29, 1986

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SUMMARY

A report is given of participation in an international meeting held in Hungary to evaluate and document the need for biological monitoring, primarily of blood and urine of workers exposed to pesticides on their job. A separate report is given on the safe use restrictions for methyl bromide as used in the soil fumigation operations in glass houses in the Netherlands.

REPORT OF TRIP TO PARTICIPATE IN AN

INTERNATIONAL WORKSHOP ON "BIOLOGICAL MONITORING OF

WORKERS MANUFACTURING, FORMULATING AND APPLYING PESTICIDES" IN

SZEGED, HUNGARY AND TO OBSERVE METHYL BROMIDE USE IN THE NETHERLANDS

APRIL 10-23, 1986

By Keith T. Maddy

May 30, 1986

THE MEETING IN HUNGARY

The Scientific Committee on Pesticides of the International Commission on Occupational Health (which is advisory to the World Health Organization) held an international workshop on the subject "Biological Monitoring of Workers Manufacturing, Formulating and Applying Pesticides". The workshop was held in Szeged, Hungary on April 15, 16, and 17th with committee meetings in Budapest on the 14th and the 18th. The Scientific Program and the list of delegates are attached.

This is the committee Dr. J. Knaak and I have been working with for several years to develop internationally acceptable protocols for studies to measure user exposure to pesticides. Since 1975 the California Department of Food and Agriculture (CDFA) Worker Health and Safety Branch (WH&S) in cooperation with Dr. Knaak developed procedures and protocols for conduct of such studies. There was some interaction with Dr. Clair Franklin of the Canadian Government on this subject. In 1980, CDFA released a guideline for the conduct of such studies which is Appendix 4 of our report HS-1046.

We provided information on our protocol and studies we had conducted in accord with it to the World Health Organization. Their recommended Standard Protocol for Field Surveys of Exposure to Pesticides was developed and released in 1982. This was an expanded version of the CDFA protocol.

In accord with our protocol, prior to 1982, the CDFA WH&S Branch had conducted mixer-loader-applicator (MLA) studies on pesticides such as: nitrofen (TOK), DEF, merfos (Folex), parathion, mevinphos (Phosdrin), 1,3-D, EDB, DBCP, alachlor, and molinate. In 1982, the WH&S Branch began requiring a number of registrant-sponsored MLA studies. These have included studies on nitrofen (TOK), triadimefon (Bayleton), flucythrinate (Payoff), fluvalinate (Mavrik), alachlor, captan, captafol, chlorthalonil, oxydemeton-methyl (MSR), endosulfan, oxadiazon, dinocap, cyromazine and cyanazine.

At the same time Dr. J. Knaak of the CDFA in cooperation with staff at the U.C. Davis, and U.C. San Francisco was developing protocols to determine

dermal absorption and dermal dose-response.

In 1984, the National Agricultural Chemicals Association (NACA) determined that it would be desirable for EPA to become involved in releasing a standard protocol for MLA exposure studies and dermal exposure studies. It was also desirable that studies already being required by CDFA would meet these EPA requirements when and if requested. They met with CDFA in May 1984 to become better acquainted with California's requirements and to discuss a proposal to encourage EPA to release standardized protocols and develop a generic data base for exposure studies. The generic data base could be used for future exposure estimates for specific types of applications andspecific formulations. Their protocol has just been published.[1]

As a result:

1) EPA now has a MLA exposure study protocol in the Federal Register receiving final comments. It is very similar to the CDFA, Canadian, and WHO protocols that preceeded it. (It is so close to the WHO protocol that studies done in accord with the WHO protocol should also be acceptable to U.S., Canada, and California.)

2) EPA and California have resolved the differences in their protocols for conducting dermal absorption studies. The new EPA guideline for these studies is acceptable to California. It may be promulgated as an EPA regulation within a year.

3) The NACA has agreed, in writing, with EPA to waive all proprietary rights to all MLA studies they have conducted. This will allow a contractor to assemble all of NACA's, CDFA's and Canada's data as well as published studies of others into a computerized generic MLA exposure data base. This will minimize future needs for MLA exposure studies of similar exposure situations with similar products.

The major focus of the 1986 international meeting in Hungary was to recognize that: 1) Most MLA exposure involves little or no inhalation or ingestion, 2) Most of the exposure is via the dermal route, and 3) the MLA exposure protocols now going into place are the current state of the art, <u>but they may often overestimate</u> the actual exposure.

<u>The overestimates</u> involve measuring the amount of pesticide that falls on the skin and then estimating from animal studies what we think is going through the skin.

This meeting focused on the need for and the manner of getting more accurate measurements of exposure through biological monitoring primarily by examining the users blood and urine for residues of the chemicals in the formulation with toxicities of possible concern.

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[1] Ronald Mull and John F. McCarthy, "Guidelines for Conducting Mixer/Loader-Applicator Studies," *Veterinary and Human Toxicology* 28, (4) (August 1986), pp. 328 -336.

This focus of the meeting was well-achieved by all concerned stating that as new pesticides are now being developed, metabolism studies are now required by the U.S., Canada and Japan which identify parent chemical and metabolite and its disposition in blood, urine, and feces through time. Since most chemical companies try to get registration in these three countries, their data requirements set the world's standards. These data on new pesticide active ingredients will allow for much more accurate estimation of exposures to users because laboratory methodology would be available to measure for the residues in blood and urine. It was proposed by some at the meeting that such data be required on all old pesticides; the concensus was, though this is desirable, it would be unrealistic to achieve.

It was emphasized that biological monitoring information was needed by the appropriate occupational health physicians world-wide. The EPA representative stated that since all metabolism data developed in animals is now available to any U.S. citizen who requests it on U.S. registered pesticides, there is no point in any registrant not providing it as a general public literature hand-out for physicians, as well as providing the laboratory methodology for the chemical in blood and urine.

The full text of all the papers presented at this meeting will be a special issue of Toxicology Letters (an international journal) this October.

Final Recommendations of the Committee Meeting

Final recommendations were prepared (See Appendix). The one of most important to California is a reaffirmation of this committee's position for the past six years on cholinesterase monitoring.

The consensus is that routine, long-term cholinesterase testing can not be ethically justified. It makes the worker the long term environmental sampling device, to identify hazardous work sites. Cholinesterase testing can, and should be required by a medical supervisor and/or a government entity whenever it appears necessary based on 1) an illness investigation, 2) a workplace inspection that identifies or leads to a suspicion of faulty workplace safety rules, supervision and compliance, or 3) the implementation of a new workplace safety program.

Baseline cholinesterase levels are ethically appropriate. A series of three tests run in a well qualified laboratory are needed to set an ideal baseline. More than 30% depression of the red cell or whole blood cholinesterase must result in removal of the worker from exposure until the baseline range is again reached. Plasma cholinesterase levels are not necessary. The type of pesticides used and the manner of their use must be immediately evaluated by the medical supervisor and the employer.

European studies have shown that in some workers with more than 30% red cell cholinesterase depression, there is definite impaired health. Just to state that the ill health appears to be reversible when exposure ceases is not an ethical position for an occupational health physician to take, especially in workers so exposed the year around. (CDFA regulations still allow 40% depression of red cell cholinesterase and 50% depression of plasma.) This international group believes that the plasma levels do not lend themselves to regulatory requirements; they are too variable with some of the newer

chemicals.

As is always the case with such meetings, the information informally obtained almost exceeded that provided in the formal presentations. I sat at the committee table between the Russian government representative and the Shell Chemical Company International Medical Director and across the table from the representative of the governments of Israel and India. A few items of this type of information are provided below:

1) Toxicity Category One (Class One) pesticides especially those that have dermal toxicities (LD_{50s}) that place them in Class One (particularly the organophosphates) - Due to concerns of deaths, poisonings and the inability to keep red cell cholinesterase levels to less than 30% depression, large areas of the world stopped using these pesticides 8 to 10 years ago. For instance very few toxicity category one pesticides and especially organophosphates (including parathion and mevinphos) are used within the USSR, in any eastern European country, in India and to some extent in Japan. This is also thought to be generally the case in China. Thus 3/4 of the world's population lives in countries where the people have decided these chemicals are too toxic to use. Even in western Europe these pesticides have only limited use under very tight restrictions. In a number of cases they are kept on the books as registered (although so tightly restricted that use does not occur) so that export of these pesticides from manufacturers and formulators from the same country is still legal.

   For example, the U.S. now finds itself in the company of only a few countries, such as Columbia, Indonesia, Thailand, Philippines, Libya, Ivory Coast, Italy and a few others with esentially no pesticide regulatory program, that still use ethyl parathion.

2) Changes in Regulatory Climate World-Wide on Pesticides - During the past five years with the developing agricultural surpluses world-wide (with a few exceptions such as north central Africa and Haiti), the arguments of agricultural and chemical interests that all pesticides need to remain registered for use has begun to be ignored on a major scale in favor of health and environmental concerns. The Danish system, already very restrictive, is now being even more tightly reorganized under new legislation. England's laws and regulations have just been drastically revised. The new format emerging in a number of countries has the civil service assembling data and suggesting registration and regulatory decisions, and then two levels of advisory committees making the <u>final</u> <u>decisions</u>. In England now, just one negative note from the Health Ministry blocks any registration. (In Malaysia they have a system very similar to the new British system.) In Malaysia, the Pesticide Advisory Committee's final decisions are not even appealable in the courts; only the King can overrule such a decision.

   Germany (with its affluence, and thus its ability to buy food from any source in the world, and with its environmental and health concerns as well as its acid rain problems) may take the lead ahead of EPA in phasing out old chemicals with presumed problems. They

recently suspended the registrations of captan, captafol, and folpet because of cancer and teratology concerns. They had the newer Chevron data which CDFA and EPA now have, but they were also influenced by a Japanese cancer study on captafol recently published.[2] An additional political factor has gained importance in Germany. In the last parliamentary election, the Green Party (a strong environmental party) got over 5% of the national vote. The small parties in that country form coalitions with other parties to get critical environmental votes from the larger coalitions they affiliate with. Since Germany is a major food importer and there is a developing world-wide medical and toxicological consensus that the data on these three chemicals hardly justifies continued use, it is expected that use of these three chemicals may soon cease in Norway, Sweden, Denmark, Holland and Hungary so they can sell food to Germany. (Some use of these three chemicals might be justified in the tropics where fungi on food crops produce aflatoxin to the extent that there is already an excess of colon cancer even with some fungal control by chemical fungicides.)

3) Alachlor - Canada took their position on the cancellation of alachlor because they do not accept the mathematical procedure of taking five days of significant exposure per year and diluting it mathematically with 365 days so that the total dose for the year appears to be negligible. Dr. Clair Franklin has stated that she does not have an alternate mathematical formula to determine when the daily (or a few days of) exposure is unacceptable.

4) Safety of Home and Garden Products - India now requires that all products formulated for such use must be <u>ready to use</u> with no mixing or further dilutions. No toxicity category one and few toxicity category two pesticides are permitted for such uses. (We in the U.S. and CDFA have considered this as a desirable requirement.)

5) Health of Greenhouse Workers - In both the USSR and eastern Europe there is developing concern about the health of persons who work in greenhouses the year around. There are concerns about enzymatic, hormonal, cardiopulmonary, and neurologic health, especially of women. In these contries, use of toxicity category two cholinesterase inhibiting chemicals, are suspect in causing these conditions even without detectable cholinesterase depression.

6) Herbicide Reentry Study in National Forests In California (to be dropped) - Dr. T.L. Lavy (from Arkansas), the international expert on blood and urine monitoring of forestry workers for herbicide residues, stated with great concern, that he planned to give up a U.S. government-sponsored study in the northern California coastal areas due to implied threats to his safety and that of his team. He believes his study (which will continue in three other states this summer) will show little or no uptake of herbicides in blood or urine of forestry workers or others who may walk through treated

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[2] Nobuyuki Ito, et.al., "Carcinogenicity of Capitol in $B6C3F_1$ Mice," *Gann* 75, (October 1984), pp. 853-865.

areas. The U.S. Forest Service wants the study conducted. The Federal Court will permit the appropriate pesticide applications and study.

As an aside, Hungary is an interesting country. (Hungary is the size of the central valley of California; with an overlay map, the border near Vienna, Austria would be at Redding, Sacramento would be over Budapest and the Russian border would be at Bakersfield.) As a result of Russia's insistence in 1949 everything was nationalized. Now except for farmland, all homes, apartments, businesses and industry are being sold back to the people at 25 cents on the dollar. Farmland, on the other hand, is considered a national resource along with their newly replanted forests, new pulp wood areas, hunting preserves and park lands. They have no individual farm ownership. They don't want to go back to the landed gentry and the peasant farmer situation of pre-1949. The "Farm Advisor" (Extension Agent type person) is the manager of farming operations consisting of several thousand acres each. The land is farmed by laboring work crews without much middle management. The National Agricultural Department determines the number of acres of various crops needed. The Farm Advisor-Manager system is responsible for: 1) area-wide planting plans to avoid monocultures, 2) promoting integrated pest management (no treament of crops for cosmetic effect is permitted except for export), 3) controlling soil erosion, and 4) staging planting to maximize use of machinery etc. Hungary may consider leasing land to growers in the future, but sale to individuals is not likely.

Hungary and Yugoslavia are reasonably prosperous and are no longer communist, and in fact are only partially socialist. Romania, east of them, on the other hand, is still under dedicated communist control; their economy is a disaster with homes not heated above 50° F in winter and they do not have enough money to buy gasoline for tractors or cars. There is a significant return to use of horses for farm work and travel.

REVIEW OF METHYL BROMIDE USE IN HOLLAND'S GLASS-HOUSES

(The land area of Holland in a map overlay would be the size of the Valley between Sacramento and Fresno.)

In summary this visit revealed:

1) All use of the rototiller injectors has been banned in glass-houses in Holland and Belguim. They proved to be far too hazardous, and resulted in many poisonings.

2) All use of cartridge respirators for such indoor applications has been banned. Supplied air respirators must be used.

3) All such glass-house applications must be made by licensed applicators.

4) Methyl bromide always contaminates the ground water below the glass house. The water table is one foot below the surface. If there is a well nearby, or any water district underground pipes nearby made of plastic such as PVC, the fumigation permit will not be signed by the local water quality agency. (In that case, the glass house operator must lay permanent pipe under the soil of the glass house and sterilize

it periodically with steam to kill pests.)

5) The drain pipes under a treated plot must be shut off for 2 weeks to keep the methyl bromide in the plot area as much as possible.

6) There are limits on the distance from the closest house to the glass house. These were set to keep air levels of methyl bromide under 50 ppb in nearby houses. These distances range from 30 to 50 meters as minimums.

7) The use of 3 mil polyethylene and a number of other plastic films to cover the soil have been banned because they were believed to be too porous, and basically worthless. A three layer Saranex film is one of the few approved films. Use of this film, properly placed, allows reentry into other areas of the glass house by unprotected workers 24 to 36 hours after completion of the application. The full fumigation process takes 7-10 days on the treated plot to kill the nematodes of concern. Some of the major crops in these glass houses are tomatoes, cucumbers and flowers.

8) After the soil is tilled, lengths of plastic tubing (of about one inch in diameter when inflated) are laid on the top of the soil about 6 feet apart. The tubing is perforated every few inches with tiny holes. These tubes that lay on top of the soil are then covered with the Saranex sheeting which is rolled out by hand along with the tubing under it. The plastic overlap areas are dampened with water mist and thus seal tightly. The methyl bromide lead-in piping is attached on one edge of the plot to each plastic pipe that goes across the plot.

9) Up to 40 grams of methyl bromide per square meter of soil are permitted in one treatment per year. Usage is kept as low as possible to minimize ground water contamination.

10) If methyl bromide is found to be a carcinogen, the ground water contamination potential may result in a ban and a return to steam sterilization.

11) All methyl bromide workers must be under medical supervision (as is also the case in England) to be sure they can wear SCBA and that they are not being overexposed; they must have at least two blood/bromine determinations per year. If the level of one worker exceeds 3 mg%, the work practices of the firm must be reevaluated. If the blood level of any workers exceeds 6 mg%, his working with methyl bromide must stop; the work practices must be inspected and upgraded. The medical supervisor may order as many follow-up blood or urine bromine analyses as he determines to be necessary. He may also inquire into all other possible sources of the bromines. In no case can routine blood or urine monitoring be instituted to keep a firm with a borderline safety program operating. Liscense suspension or fines imposed by the Labor Inspectorate (Dutch "OSHA") are in order.

12) All blood or urine bromine analyses for occupational exposure monitoring must be submitted to the one laboratory in the country certified for conduct of such tests.

13) As a result of information developed on poisonings and low grade illness conditions from exposure to methyl bromide before the country's program was tightened, considerable concern developed in the medical community about overexposure.

14) The TLV for all workplace exposures for methyl bromide is now being dropped to 5 ppm in Holland. In reality the Labor Inspectorate requires applicators and tarp pullers to wear SCBA. They have studied in detail the levels of this chemical in the air as it moves geographically away from the treated area, through time. They do not intend to allow any other workers to be exposed to more than 1 ppm and the Public Health Department does not want the general public to be exposed to more than about 50 ppb for more than a few hours.

15) Chloropicrin use is not permitted in Holland as a fumigant or as a warning agent. They say it dissipates too soon and then gives a false sense of security that the "fumigant" is gone.

In the two days available in Holland, I was able to talk to the owner of a major PCO firm, to three applicators (workers) and several staff members of the Labor Inspectorate as to various viewpoints on the continued use of methyl bromide in greenhouses.

In general, the users are walking a tight rope over 1) water contamination concerns, 2) worker poisoning potential, 3) worker and employer concerns that the inhalation studies now underway may show methyl bromide to be a carcinogen, and 4) public health concerns of homeowners who live next to glass houses.

The current glass house fumigation procedure if <u>carefully</u> followed, can result in keeping the applied dose of methyl bromide much lower than was previously needed when used under leaky tarps. The higher doses used previously resulted in more ground water contamination than at doses used now. The better tarps allow non-fumigation workers back into the glass house in a day or two while the tarps are still in place.

I was provided with a considerable amount of printed literature by the Dutch government about methyl bromide and I have a number of photographs of the process.

SCIENTIFIC COMMITTEE ON PESTICIDES
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10 March, 1986

7TH WORKSHOP "BIOLOGICAL MONITORING OF WORKERS MANUFACTURING, FORMULATING AND APPLYING PESTICIDES"

SZEGED, HUNGARY, 15-17 APRIL 1986

Provisional list of participants

Dr. K. Barabas
Institute of Hygiene and Epidemiology, University Medical School, Szeged, Hungary

Dr. J. Bonsall
FBC Ltd., Hauxton, U.K.

Dr. J. Burgess
Director of Occupational Medicine, Dow Chemical Company Limited, Hunstanton, U.K.

Mr. G. Chester
ICI PLC, Plant Protection Division, Haslemere, U.K.

Dr. J.F. Copplestone
Chief, Pesticide Development and Safe Use, Division of Vector Biology and Control, World Health Organization, Geneva, Switzerland

Prof. Dr. I. Dési
Director, Institute of Hygiene and Epidemiology, University Medical School, Szeged, Hungary

Dr. C.A. Franklin
Chief, Environmental and Occupational Toxicology Division, Ottawa, Canada

Dr. R. Grover
Research Station, Agriculture Canada, Regina, Canada

Dr. R. Gun
South Astralian Health Commission, Adelaide, South Australia

Dr. T.B. Hart
Product Safety Auditor, ICI PLC, Plant Protection Division, Haslemere, U.K.

Mrs. E.A.H. v. Heemstra-Lequin
Health, Safety and Environment division, Shell Internationale Petroleum Maatschappij B.V., The Hague, The Netherlands

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Senior Environmental Specialist, CIBA-GEIGY, Agriculture Division, Greensboro, USA

Dr. A. Inkmann-Koch
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Dr. J. Jeyaratnam ?
National University of Singapore, Department of Social Medicine and Public Health, Singapore, Singapore

Dr. S.K. Kashyap
Officer-in-charge, National Institute of Occupational Health, Ahmedabad, India

Prof. B. Kolmodin-Hedman
National Board of Occupaitonal Safety and Health, Medical Division, Umea, Sweden

Dr. L. Kozo
Chief veterinarian doctor, Ministry of Agriculture, Szeged, Hungary

Dr. R. Kummer
Health, Safety and Environment division, Shell Internationale Petroleum Maatschappij B.V., The Hague, The Netherlands

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University of Arkansa, Department of Agronomy, Altheimer Laboratory, Fayetteville, USA

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Occupational hygienist, Kuopio Regional Institute of Occupational Health, Kuopio, Finland

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Director Hygiene and Epidemiology Station County, Csongrád, Hungary

Prof. Dr. C.D. Pfaffenberger ?
University of Miami, Miami, USA

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Chief, Special Review Section, Exposure Assessment Branch, Hazard Evaluation Division, Office of Pesticide Programs, The Environmental Protection Agency, Washington D.C., USA

Dr. E. Richter
Department of Medical Ecology, Hebrew University Medical School, Jerusalem, Israel

Prof. Dr. L. Rosival
Director, Centre of Hygiene of the Research Institute of Preventive Medicine, Bratislava, Czechoslovakia

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Dr. M. Székely
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SCIENTIFIC COMMITTEE ON PESTICIDES
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SEVENTH INTERNATIONAL WORKSHOP
"BIOLOGICAL MONITORING OF WORKERS MANUFACTURING, FORMULATING AND APPLYING PESTICIDES"

15, 16 and 17 April 1986, Szeged, Hungary

Scientific programme

For each presentation or topic, 40 minutes have been allocated. Speakers are urged to allow for extensive discussion by restricting their formal presentation to 20-25 minutes.

TUESDAY 15TH APRIL

09.00	**Welcome**	Dr. M. Palotás, Director Hygiene and Epidemiology Station County, Csongrád Prof. Dr. I. Dési, University Medical School, Szeged; local host Dr. W.F. Tordoir, Shell Internationale Petroleum Maatschappij B.V., The Hague; Chairman of the Workshop
	Opening address	Prof. Dr. L. Rosival, Director Centre of Hygiene of the Research Institute of Preventive Medicine, Bratislava Chairman of Scientific Committee on Pesticides
	Personal introductions	Participants
10.20	**Specific features of the changes in the health status of greenhouse female workers exposed to pesticides**	Prof. Dr. Yu.I. Kundiev, Research Institute of Labour Hygiene and Occupational Diseases, Kiev
11.00-11.20	Coffee break	
11.20	**Biological monitoring and health surveillance of a group of greenhouse pesticide sprayers**	Prof. Dr. I. Dési, University Medical School, Szeged

12.00 **Erythrocyte storage enzyme activity and hemoglobin-conjugates as a principle of biological monitoring for pesticides**
Dr. J. Lewalter, Bayer AG, Leverkusen-Bayerwerk

12.40-14.00 **Lunch break**

14.00 **Use of biological monitoring in the estimation of exposure during the application of pesticides**
Dr. C.A. Franklin, Environmental Health Directorate, National Health and Welfare, Ottawa

14.40 **Monitoring the urine of pesticide applicators in California for residues of chlordimeform and its metabolites 1982-1985**
Dr. K.T. Maddy, California State Department of Food and Agriculture, Sacramento

15.20-15.40 **Tea break**

15.40 **Progress in pesticide exposure studies and future concerns**
Dr. T.L. Lavy, University of Arkansas, Fayetteville

16.20 **The UNDP-sponsored European epidemiological study on the health effects of exposure to organophosphorus pesticides**
Prof. Dr. M. Maroni, University of Milan, Milan

WEDNESDAY 16TH APRIL

09.00 **Biological monitoring of greenhouse workers' exposure to organophosphorus pesticides**
J. Liesivuori, M.Sc., Kuopio Regional Institute of Occupational Health, Kuopio

09.40 **Cholinesterase and monitoring of exposure-absorption**
Dr. E. Richter, Hebrew University Medical School, Jerusalem

10.20 **Biochemical aspects of monitoring of exposure and health effects during field application of insecticides**
Dr. N.J. van Sittert, Shell Internationale Petroleum Maatschappij B.V., The Hague

11.00-11.20 **Coffee break**

11.20

12.00 **Field studies on health effects from the application of organophosphorus formulations by hand-held ULV to cotton**
Dr. R. Kummer, Shell Internationale Petroleum Maatschappij B.V., The Hague.

12.40-14.00 **Lunch break**

14.00 **Biological monitoring for organophosphorus induced delayed polyneuropathy**
Prof. Dr. M. Lotti, University of Padova, Padova

14.40 Spare

15.20 **Tea break**

City tour

THURSDAY 17TH APRIL

09.00 **Biological monitoring and health surveillance of pesticide formulators in India**
Dr. S.K. Kashyap, National Institute of Occupational Health, Ahmedabad

09.40 **Biological monitoring of a herbicide applied through backpack and vehicle-sprayers**
Dr. T.B. Hart and G. Chester, ICI PLC, Haslemere

10.20 **A critical evaluation of 2,4-D excretion patterns in urine of farmers using ground rigs**
Dr. R. Grover, Research Station, Agriculture Canada, Regina

11.00-11.20 **Coffee break**

11.20 **The safety evaluation of bendiocarb, a residual insecticide for vector control**
Dr. J. Bonsall, FBC Ltd., Hauxton

12.00 **National Agricultural Chemicals Association: Overview on assessment of mixer-loader-applicator exposure to pesticides**
Dr. R. Honeycutt, CIBA-GEIGY, Greensboro, USA

12.40-14.00 **Lunch break**

14.00 **Guidelines for the registration of pesticides in the US in relation to exposure assessment**
Dr. J.C. Reinert, The Environmental Protection Agency, Washington, D.C.

14.40 **Some observations on the biological monitoring of pesticide workers**
Dr. J.F. Copplestone, World Health Organization, Geneva

15.20-15.40 **Tea break**

15.40 **Report of rapporteur. Recommendations to the International Commission on Occupational Health**

17.00 **Closing remarks** Prof. Dr. L. Rosival

Workshop officers

Local hosts : Dr. M. Palotás
Prof. Dr. I. Dési

Local secretary: Dr. K. Barabas

Chairman : Dr. W.F. Tordoir
Co-chairman : Prof. Dr. L. Rosival
Rapporteur : Dr. N.J. van Sittert

Scientific editors of the proceedings:
Mrs. Drs. E.A.H. van Heemstra-Lequin
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09.04.86

SCIENTIFIC COMMITTEE ON PESTICIDES
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Secretariat
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23rd April 1986

Dear Dr. Maddy,

The VIIth International Workshop of the Scientific Committee on Pesticides of the International Commission on Occupational Health (ICOH), Szeged, Hungary, April 15-17, 1986.

Report of rapporteur

Please find enclosed a copy of the draft manuscript 'report of rapporteur'. In case you have any comment, we would appreciate receiving this before 16 May 1986. If you do not agree with a text, please provide alternative language, i.e., the full text which you would like to see incorporated in the report.

Yours Sincerely,

Dr. N.J. van Sittert

cc: Dr. W.F. Tordoir
Mrs. Dr. E.A.H. van Heemstra-Lequin

SCIENTIFIC COMMITTEE ON PESTICIDES

OF THE INTERNATIONAL COMMISSION ON OCCUPATIONAL HEALTH

VIIth INTERNATIONAL WORKSHOP

SZEGED, HUNGARY, APRIL 15-17, 1986

REPORT OF RAPPORTEUR

N.J. van SITTERT

PREFACE

The VIIth International Workshop of the Scientific Committee on Pesticides of the International Commission on Occupational Health (ICOH) was held in Szeged, Hungary, on April 15-17, 1986.

The subject 'Biological monitoring of workers manufacturing, formulating and applying pesticides' was chosen in view of the WHO standard protocol VBC/82.1 on 'Field surveys of exposure to pesticides', in which biological monitoring had been incorporated as a method for monitoring the exposure to pesticides. The aim of the workshop was to discuss the present state of the art of biological monitoring of human exposure to pesticides, to identify specific advantages and limitations and to formulate recommendations for the ICOH. Thirty-three invited experts from 14 countries working in international organizations, governmental agencies, academia, or industry, discussed 16 papers. One paper could not be presented but will be included in the Proceedings.

The workshop was held in the Hygiene and Epidemiology Station of the county of Csongrád, Szeged.

OPENING SESSION

Dr. M. Palotás, director of the Hygiene and Epidemiology Station, Prof. I. Dési, chief, Institute of Hygiene and Epidemiology, University Medical School, Szeged, Prof. V. Varró, deputy rector, University Medical School, Szeged, and Dr. W.F. Tordoir, secretary and treasurer of the Scientific Committee and chairman of this workshop welcomed the participants.

In his opening address, Prof. L. Rosival, chairman of the Scientific Committee on Pesticides, referred to the WHO standard protocol VBC/82.1, which has been prepared in close cooperation with the Scientific Committee during a small workshop in The Hague, in 1981, and to the definition of biological monitoring, defined and accepted in 1980 by the NIOSH, the OSHA and the EEC-Health and Safety Directorate during a symposium on 'Assessment of toxic agents at the workplace: 'Roles of ambient (environmental) and biological monitoring' (1). Biological monitoring was defined as 'the measurement and assessment of workplace agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these to evaluate exposure and health risk compared to an appropriate reference'.

Prof. Rosival mentioned the advantages of biological monitoring as a method to evaluate occupational exposure to pesticides:

1. it determines the total absorption via all routes of exposure;
2. it assesses differences in absorption and toxicokinetics between individual persons;
3. it also measures non-occupational exposures;

4. it is a check on the personal hygiene and the use and efficiency of personal protection;
5. it takes into account the impact of physical activity on respiratory intake and the impact of hot and humid conditions on dermal absorption.

As current specific problems, Prof. Rosival highlighted the complexity of some of the analytical methods and the lack of quality assurance programmes.

SCIENTIFIC PROGRAMME

The papers presented during the scientific programme can be grouped as follows:

1. ten papers reviewed the application of biological monitoring in field studies, in greenhouse studies, in a formulation and manufacturing plant study and in a planned epidemiological study under auspices of the United Nations Development Programme (UNDP);
2. two papers were presented on the relationship between dermal exposure and urinary metabolite concentrations in humans;
3. two papers dealt with the development of new biochemical tests for monitoring worker's exposure to pesticides;
4. two papers discussed the development of protocols for conducting exposure monitoring studies in a regulatory context. These were presented by representatives of the U.S. Environmental Protection Agency (EPA) and the National Agricultural Chemical Association (NACA) in the U.S.

1. Application of biological monitoring in practice

The application of biological monitoring in field studies and in studies in greenhouses was discussed in eight papers. These dealt with monitoring of workers exposed to organophosphorus pesticides, organochlorine pesticides, herbicides, pyrethroids and carbamates. In one paper devoted specifically to organophosphorus pesticide exposure, it was shown that the measurement of urinary alkylphosphate and p-nitrophenol concentrations is a more sensitive method for monitoring exposure than the measurement of whole blood, red blood cell or plasma cholinesterase activity. In another study dealing with organophosphorus pesticide exposure, serial determinations were carried out pre-season and in season in a group of residents and in a group of field workers. It was shown that the field workers had greater fluctuations within normal limits for whole blood and plasma cholinesterase activities compared with the residents.

One paper was presented on the monitoring of occupational exposure to the toxic pesticide chlordimeform by the measurement of its urinary metabolite concentration. Because of the extensive use of biological monitoring the efficacy of personal protection during application of this pesticide could be checked.

Biological monitoring of workers specifically exposed to a carbamate was discussed in one paper. An important conclusion was that the routine measurement of blood cholinesterase activity is not useful or reliable after carbamate exposure because inhibition is rapidly reversible. The study also showed the importance of sampling blood for cholinesterase monitoring from an uncontaminated source.

Two studies dealt with the biological monitoring of the chlorophenoxy- acetic acids 2,4-D and 2,4,5-T. These studies pointed out the inherent variability encountered in subjects and operational conditions when sampling under actual field spraying situations. The excretion rate of 2,4-D in urine was dependent on the number of exposures, the time interval between exposures and the amount of active material sprayed. It varied from 4-7 days after the last exposure. Dermal absorption accounted for the larger part of the absorbed dose.

In two papers, the application of biological monitoring in greenhouse workers was presented and discussed. Workers were exposed to organophosphorus pesticides as well as to carbamates and pyrethroids. In one study the cholinesterase activity was inhibited in the group of exposed workers compared with the controls, but in the other paper no significant changes were measured. In addition, in the latter paper no changes in certain immunological blood tests were reported.

Only one paper in this workshop dealt with biological monitoring of workers engaged in manufacture and formulation of pesticides. Formulation workers who were exposed to a specific organophosphorus pesticide, showed inhibited whole blood and plasma cholinesterase activities; however, red blood cell cholinesterase activities remained within normal limits. In workers exposed to the organochlorine hexachlorocyclohexane (HCH), the concentration of beta-HCH in serum was higher than that of alpha- and gamma-HCH. Formulation workers had higher serum HCH concentrations than manufacture workers.

In one paper the biological monitoring methods were discussed which will be used in a large multinational study to evaluate exposure to organophosphates and to assess the possible long term health risks. This study is being designed under the auspices of the United Nations Development Program (UNDP) with assistance from the WHO, Regional Office Europe. Biological monitoring will consist of the determination of red blood cell and plasma cholinesterase activity and the determination of the concentrations of urinary alkylphosphates and/or p-nitrophenol. In addition, serum paraoxonase activity and lymphocyte neuropathy target esterase (NTE) are indicated in the protocol as optional biochemical tests. An important spin-off of this study is the permanent cooperation between scientific institutes of different countries, the standardization of analytical methods for biological monitoring and the start of an interlaboratory quality assurance programme.

2. Studies relating dermal exposure to urinary metabolite concentrations

Two papers were presented on this subject. In the first paper, this relationship was determined for an organophosphorus pesticide. In controlled laboratory studies, the correlation between the amount of alkylphosphate metabolite in the urine and the amount of parent compound applied to the skin was found to be linear and the ratio of metabolite to parent compound was similar in both rats and humans. In field studies where dermal patches and urinary metabolites were used to estimate dermal exposure, the urinary metabolite levels provided a more reliable estimate. Additional data was presented in which dermal penetration studies done in a variety of species showed that there was substantial species variability.

The second paper dealt with the generation of personal exposure/absorption data, using a WHO recommended 'whole body' method (overalls, gloves) and determination of urinary metabolites, after application of a herbicide. In the first instance, this was done for backpack sprayers. From the data obtained, the systemic absorption following application with vehicle sprayers was estimated using 'percentage absorption' and 'rate of absorption' models. Exposure and absorption following vehicle application were then measured and the validity of the models assessed. The 'rate of absorption' model gave a more reliable estimation than the 'percentage absorption' model.

3. The development of new biochemical tests for monitoring pesticide exposure

Two papers dealt with this subject.

The first paper concerned the determination of erythrocyte-adducts formed by reaction of a pesticide or its reactive intermediate with erythrocyte proteins. This approach allows a better estimate of the active dose which may be delivered at the target organ, and, therefore, may provide a better individual risk assessment of exposure to chemicals than the determination of the chemical or its metabolite(s) in body fluids. Examples were given of adduct formation in the erythrocytes of subjects exposed to aromatic amines containing herbicides and to a carbamate. In workers exposed to the carbamate, good correlation has been shown between the inhibition of red blood cell cholinesterase activity and the amount of erythrocyte-adduct. The second paper dealt with the determination of NTE activity in lymphocytes for the biomonitoring of organophosphorus induced delayed neurotoxicity

(OPIDN). So far, in poisoning cases it has been shown that the NTE activity in the lymphocytes correlates with that in the nervous tissue and that the lymphocyte NTE inhibition has predictive value for OPIDN. The value of measuring NTE activity in lymphocytes in occupationally exposed workers needs further study.

4. The development of protocols for conducting exposure monitoring studies

Two papers dealt with this subject.

The first paper was presented by a representative of the NACA. A protocol has been developed for performing field worker exposure studies, which has been published in 1985. In the protocol, emphasis is given to the measurement of dermal exposure using the patch method rather than using biological monitoring. The latter technique, however, will be further developed. In addition, NACA, EPA and NHW (Canada) have agreed to develop jointly a generic exposure data base.

The second paper was presented by a representative of EPA. Draft guidelines for the conduction of exposure monitoring studies were discussed. The advantages and disadvantages of both biological monitoring and passive dosimetry were highlighted. The use of biological monitoring methods will be encouraged in the guidelines. Finalized guidelines will become available in 1986.

DISCUSSION

Highlights of the general discussion and the discussion of the individual papers are the following.

- It was recognized that a major problem for the use of biological monitoring is the lack of human data relating directly the parameter(s) used in biological monitoring to the possible biological effect(s). This hampers the establishment of biological limit values. This problem may be overcome by carrying out prospective and retrospective epidemiological studies and by collecting data from poison control centres. An example of such a prospective epidemiological study is the study on organophosphorus pesticide exposure, which is being designed under the auspices of UNDP. Another possibility lays in the understanding of the mechanism of action and on the accessibility of the target. Blood cholinesterases, and possibility NTE, represent a good example of biochemical tests with sound rational basis.

However, at present, in most cases the dose-effect relationships as identified in the animal model, have to be used to assess the health risk for men. This implies that the parameter(s) used in biological monitoring (for instance the amount of urinary metabolite excreted in a given time) has/have to be translated in terms of an oral dose and a dose applied to the skin. Well controlled human volunteer studies are the only method to relate a defined dose to the parameter(s) used in biological monitoring. The dose has to be applied either orally or dermally. For the latter the use of radiochemicals is recommended.

- It was recognized that in most countries field studies are not yet required by regulatory bodies for pesticide registration. Some countries, however, have specific requirements for such studies including patch data and biological monitoring.

- It was realized that in this workshop also biochemical tests were discussed which do not fall under the definition of biological monitoring as accepted by the NIOSH, the OSHA and the EEC - Health and Safety Directorate. However, it was agreed that it is not necessary to strictly adhere to this definition, as long as it is clear what the objective of a test is.

- In that context, tests for health effect screening were not considered as biological monitoring because, firstly, such tests indicate a biological effect which probably is not agent-specific and, secondly, reflect a health condition rather than an estimation of absorbed dose.

- Unpublished biological monitoring methods should be made available to third parties if these methods are used in occupational health. The proprietary nature of these methods should be respected and acknowledged.

- It was discussed that in biological monitoring studies the amount of metabolite excreted in the urine is noted in many different ways such as mg/l, mg/h, mg/g creatinine, mg/24 h, mg/kg body weight, mg/kg active ingredient sprayed. For the comparability of urinary metabolite excretions from different studies, either uniformity in data presentation is required, or all relevant data should be provided.

RECOMMENDATIONS

1. For the definition of biological monitoring it is recommended to extend the terminology as defined and accepted by NIOSH, OSHA and the EEC-Health and Safety Directorate during the Symposium on 'Assessment of toxic agents at the workplace; roles of ambient (environmental) and biological monitoring' (1). In the context of pesticide exposure monitoring it is practical to include biochemical tests, which are compound specific or are specific for a group of compounds, under the definition of biological monitoring, e.g., the determination of whole blood, red blood cell and plasma cholinesterase activity in exposure to organophosphorus pesticides.

2. Biological monitoring, as defined in recommendation number one, is the preferred and usually most sensitive method for monitoring the total absorbed dose. Biological monitoring is particularly suitable for the monitoring of exposure to pesticides because of the various routes of exposure (mainly dermal), and the possible combination of occupational and non-occupational exposure.

3. Greater attention should be given during the development of the toxicological database to (i) obtaining data to relate toxic effects not only to the administered dose but also to the parameter(s) used in biological monitoring, e.g., urinary metabolite levels; and (ii) identifying species differences in pharmacokinetics (absorption, distribution, metabolism, bioaccumulation and excretion).

4. There is a need for the establishment of biological limit values, supported, whenever possible, by epidemiological data. In addition, appropriate background (reference) values should be established for non-occupationally exposed humans.

5. Studies under closely controlled conditions should be performed in human volunteers, relating defined oral and dermal doses to the parameter(s) used in biological monitoring. These studies should be carried out in accordance with legal and ethical requirements and should observe relevant national and international codes of conduct.

6. Whenever possible, the information on biological monitoring parameters available from poisoning cases should be used to increase our knowledge of the human toxicology of the causative agents.

7. The dermal patch method and biological monitoring are not mutually exclusive, but are complementary. For the assessment of dermal absorption, dermal exposure as determined with exposure pads should be correlated with the relevant biological monitoring parameter.

8 a. Further development and validation of compound specific or group-of-compounds-specific biological monitoring methods for the assessment of exposure to pesticides is necessary.

8 b. In order to determine the value for health risk assessment of new biochemical tests which recently have been developed, or are still under development, and which were discussed in this workshop, i.e., (i) the determination of the amount of hemoglobin adducts, (ii) the measurement of NTE activity in lymphocytes and (iii) the measurement of paraoxonase activity and other organophosphorus pesticides hydrolyzing enzymes in serum, there is a need to validate these by well designed and carefully performed studies.

9. To obtain reliable results, particular attention has to be given to the quality of the sample and the analytical variation of the method. Contamination of the sample has to be avoided, e.g., after exposure to cholinesterase inhibitors venous blood should be collected, whenever possible.

10. For the comparability of biological monitoring results it is recommended that validated methods should be used, whenever possible. Internal and external quality control programmes should be developed to check the analytical variations of the method. Existing external quality assurance programmes, e.g., for plasma cholinesterase and urinary alkylphosphates should be extended to institutes using these tests.

11. Unpublished analytical methods and relevant procedures for biological monitoring, for use in occupational health, should be made available on request to third parties. The proprietary nature of such methods and procedures should be recognized and respected, if so requested.

12. During the last years more data have become available on whole blood, red blood cell and plasma cholinesterase activity in workers following exposure to organophosphorus pesticides. The guidelines with respect to suspensory action of workers, given in recommendation number five of the Vth International Workshop of the Scientific Committee on Pesticides should remain unchanged (2).

This recommendation reads: 'Many years of experience with cholinesterase determination in a wide variety of circumstances of organophosphorus exposure has indicated that, for the avoidance of acute effects, a person should cease to be exposed to these compounds when the whole blood, or red cell cholinesterase activity falls more than 30% below a well established (mean of 3 tests) pre-exposure value, until the value rises to 80% of the pre-exposure value. Significant depressions of plasma cholinesterase on their own indicate exposure but should not lead to suspensory action. They nevertheless indicate a need for reviewing of safety precautions'.

13. Data from biological monitoring studies should be used to promote and evaluate activities which are aimed at the reduction of exposure, such as improved packaging, specific formulations and training of applicators.

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